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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/486,069	06/07/1995	DEAN ENGELHARDT	ENZ-5(D8)(C2	6278

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EXAMINER	
MARSCHEL, ARDIN H	
ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 09/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 08/486,069	**Applicant(s)** ENGELHARDT ET AL.	
	Examiner Ardin Marschel	**Art Unit** 1631	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 07 July 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.
   b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): See attached summary.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: *See attached summary*.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1723,1724,1740,1741,1769-1773 and 1775*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See attached further explanation.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

DETAILED ACTION

Summary of rejections that have been overcome from the attached Advisory action, item # 5:

NEW MATTER rejection of claims 1500-1503

Vagueness and indefiniteness rejection of claims 1436-1439 and 1441-1444

Summary of allowed claims from the attached Advisory action, item # 7:

Claims 569-571, 573-575, 577, 582-589, 592-594, 597-600, 602-604, 607, 608, 610-612, 614-624, 634, 635, 637, 638, 641, 642, 646, 648-651, 656-661, 667, 670, 707-714, 716, 717, 719-723, 725-727, 729, 734-747, 749-752, 754-756, 759, 760, 762-764, 766-776, 786, 787, 789, 790, 793, 794, 796, 797, 800-803, 808-813, 819, 822, 859-866, 868, 869, 871-875, 877-879, 881, 886-899, 901-904, 906-908, 911, 912, 914-916, 918-928, 938, 939, 941, 942, 945-947, 949, 952-955, 960-965, 971, 974, 1011-1018, 1020, 1021, 1023-1027, 1029-1031, 1033, 1038-1051, 1053-1056, 1058-1060, 1063, 1064, 1066-1068, 10701080, 1090, 1091, 1093, 1094, 1097-1099, 1101, 1104-1107, 1112-1117, 1123, 1126, 1163-1170, 1172, 1173, 1175-1179, 1181-1183, 1185, 1190-1200, 1204, 1208, 1209, 1212-1216, 1218-1244, 1248, 1249, 1253, 1255-1258, 1263-1270, 1272, 1275, 1278-1294, 1296, 1297, 1411-1439, 1440-1442, 1445-1487, 1490, 1491, 1493-1499, 1504-1516, 1518, 1520-1525, 1527, 1530-1539, 1541, 1544-1568, 1570-1581, 1700-1722, 1727-1739, 1742-1757, 1760-1768, and 1776-1795 are allowed.

Further explanation of item # 11 on the enclosed Advisory action:

The rejection of claims 1723, 1724, 1740, 1741, 1769-1773, and 1775 based on NEW MATTER regarding same or different indicator molecules as utilized within a single sequencing gel methodology is maintained and reiterated from the previous office action, mailed 5/25/05.

Applicants argue that nucleic acid sequencing is just another form of nucleic acid detection in REMARKS, filed 7/7/05. In response, the above NEW MATTER different indicator molecules is found only disclosed in specific methods such as karyotyping as filed. Also, the phrase "same or different indicator molecules" is not disclosed regarding even karyotyping upon review again in connection with said REMARKS, filed 7/7/05.

Applicants point to Example 9 regarding the usage of different colored fluorescent dyes and different colored labels in other uses. Consideration of said Example 9 which occurs on pages 46-52 of the instant disclosure as filed reveals that three procedures are described listed as I. Karyotyping; II. Diagnosis of Genetic Disorders; and III. Microorganism Detection and Identification. In the Karyotyping section I, a human gene library of 100-200 clones is selected and labeled to locate hybridization to chromosomes via fluoresence wherein several sets of labeled clones are utilized. It is noted that there is no disclosure therein of the fluorescent dyes being either the same or different. Each labeled clone set is separately applied to the chromosomes being visualized. Plural digitized images are disclosed to determine if the chromosomes are suitably spread. Such plural images would only be needed if separate labeled clone hybridization to chromosomes were not distinguished as to color so as to obtain data for each added chromosome labeling at the application of each clone set by difference. This is not set forth, however, and alternatively, different colors may be utilized for each clone set in order to distinguish different chromosomal targets.

This disclosure therefore implies either that the same labels are utilized sequentially in one citation and that different colored labels may be utilized in another citation regarding first and second fluorescent dyes. Such implication disclosures are confusing within this example. Implications are reasonably statements of obviousness of disclosure which does not rise to written description. Similarly, the portion of Example 9 directed to II. Diagnosis of Genetic Disorders is suggestive of two sets of labels which may be different for chromosomes 21 and 23 with a ratio determined. The simultaneous application and measurement of two labels is not disclosed therein. Similarly, the portion of Example 9 directed to III. Microorganism Detection and Identification there is therein no disclosure of simultaneous label practice. In particular single labelled structures are described without multiply labeled DNA or bacteria. The counting of bacteria immobilized on a slide via counting the number of fluorescent spots is disclosed therein but not that such a number of spots contain different indicator labels. At best again this may be viewed as suggested which falls short of written basis for the above specific NEW MATTER phrase. The remainder of pages 50-52 disclose single label usage in particular biotin labels but do not indicate any generic usage of the labeling methodology as in portions I , II, or III of Example 9 to extend such usage to sequencing or any other methods as argued by applicants. Thus, this argument is non-persuasive.

Then on page 152-156 of REMARKS, filed 7/7/05, applicants argue further that non-radioactively labeled nucleotides etc. are instantly disclosed in a number of different processes and that inventive features are not mentioned in the instant disclosure as filed as being utilized in one process to the exclusion of other. In response, consideration of the instant disclosure as filed "also" lacks mention of utilizing inventive features in multiple processes. Instead, plural processes are described each with its

own inventive features. Applicants then point to various pages of the specification, such as pages 6, 84, and 29 as disclosing various uses of the modified nucleotides of the instant invention but none of them providing written basis for simultaneous usage of either the "same" or "different" modified nucleotides as being generic or directed to all of the disclosed processes. The footnote, for example, on page 153 of applicants' arguments regarding page 29 of the specification only cites a biotin system which is a single label practice and does not cite either the same or different labels for separate targets, for example. The citation from page 84 cites a self-signaling molecule (singular) which lacks written basis for indicator molecules (plural) either the same or different. Confusingly, applicants then argue by setting forth an interpretation of "different fluorescent labels" from this passage which clearly only describes a "self-signaling molecule" (singular). Example 9 is then re-argued in said REMARKS but has already been responded to above. This Example 9 response is reiterated from above as being non-persuasive. It is also reiterated that nothing in the Example 9 disclosure, even if reasonably interpreted as disclosing different indicator molecules, either discloses or even suggests that the labeled clones described therein could or should be utilized in any other procedure. Example 9 is additionally directed to chromosomal target identification via labeled clones. Chromosomes are well known to be vastly lengthy nucleic acids with multiple regions, gene targets, etc. therein and the usage of plural labeled clones for analysis of such large nucleic acids to locate what is clearly separate and different targets may reasonably be easily envisioned by someone of skill in the art. Sequencing procedures, on the other hand, utilize short segments of nucleic acid which only must be visualized to be detected on a gel which already has separated such segments. Internal targets within such sequencing segments are of no interest in sequencing procedures and thus are very different as to labeling needs compared to

chromosomal analysis as in said Example 9. Therefore, labeling utilized in multitarget chromosome analysis is not applicable to sequencing procedures.

Thus, in summary, this NEW MATTER rejection is still deemed proper and is maintained.

The request for Interference remains held in abeyance as the above issue still prevents proceeding with Interference proceedings.

Applicants are also reminded that a second submission under 37 CFR 1.129(a) remains available.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the Central PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The Central PTO Fax Center number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ardin Marschel, Ph.D., Supervisory Patent Examiner, whose telephone number is (571) 272-0718. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instrument Examiner, Tina Plunkett, whose telephone number is (571) 272-0549.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

September 5, 2005

Ardin H. Marschel 9/5/05

ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER